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## COMMUNITY-ACQUIRED PNEUMONIA IN ADULT AND ELDERLY POPULATIONS

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The National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health is committed to furthering scientific knowledge regarding the etiology, epidemiology, assessment, and management of emerging and reemerging infectious diseases. Consequently, NIAID is sponsoring a continuing medical initiative entitled "Emerging and Reemerging Infectious Diseases." This endeavor is designed to provide healthcare professionals with the most current information on a number of infectious diseases, including respiratory tract infections, sexually transmitted diseases, food- and water-borne infections, and HIV/AIDS.

The first program in this endeavor was a conference on "Community-Acquired Pneumonia in Adult and Elderly Populations." This conference took place in Washington, DC, on June 3 and 4, 1998. It brought together 22 nationally recognized experts in the topic area; the co-chairmen for the program were Dr. John Bartlett, Professor and Chief, Division of Infectious Diseases at Johns Hopkins University School of Medicine, and Dr. Timothy Murphy, Professor and Director, Division of Infectious Diseases, State University of New York at Buffalo. Ortho-McNeil Pharmaceutical provided an unrestricted educational grant to support the conference.

### INTRODUCTION

The past decade has seen dramatic changes in the etiology, diagnosis, and management of community-acquired pneumonia (CAP). Emerging pathogens have been identified as causative agents; when combined with the growth of antimicrobial resistance, diagnosis and management of CAP have become an increasing challenge to clinicians. Furthermore, the aging of our population has resulted in a greater number of adult and elderly individuals "at risk" for CAP.

**New antimicrobial agents have been introduced that have a broader spectrum to encompass the emerging pathogens, as well as efficacy against drug-resistant strains.**

The traditional management of CAP is no longer applicable in light of these changes. New antimicrobial agents have been introduced that have a broader spectrum to encompass the emerging pathogens, as well as efficacy against drug-resistant strains. Prevention approaches include knowledge about regional etiology and epidemiology, drug-resistance patterns, and the use of traditional and evolving vaccines. Whereas empiric therapy is often initially used, this approach can be enhanced with the use of pathogen-specific antimicrobials to reduce morbidity and mortality.

### LEARNING OBJECTIVES AND TARGET AUDIENCE

Upon completion of this program, participants will be able to:

- Discuss the changing etiology and emerging pathogens associated with community-acquired pneumonia (CAP)
- Describe the consequences of the growth of antimicrobial resistance on the management of CAP
- Identify the benefits and disadvantages of both traditional and newer antimicrobial agents
- Discuss the role of vaccines in the prevention/management of CAP.

Target Audience: Primary Care Physicians, Infectious Disease Specialists, Pulmonary Specialists

This activity should take approximately 1.5 hours to complete.

### AN EVIDENCE-BASED APPROACH TO COMMUNITY-ACQUIRED PNEUMONIA: WHAT WE KNOW AND WHAT WE DO NOT KNOW

Community-acquired pneumonia affects four million individuals annually, and is responsible for greater than one million hospitalizations. An examination of the research indicates wide variations in the management of CAP, including differences in hospital admission rates, length of hospital stay, performance of microbiological testing, and selection and initiation of antibiotic therapy. Michael Fine, MD, offered a definition of community-acquired pneumonia as "an infection of the lower respiratory tract characterized by acute signs or symptoms, which may include both respiratory and nonrespiratory symptoms; the presence of a new radiographic infiltrate; and acquisition of the infection from outside the confines of a hospital" (Table 1). He identified the four most important clinical decisions

**TABLE 1**  
**DEFINITION OF CAP**

CAP is an infection of the lower respiratory tract characterized by:

- (1) acute signs or symptoms
- (2) new radiographic pulmonary infiltrate
- (3) acquisition of infection from outside the confines of a hospital

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that must be made when confronted with a patient presenting with signs or symptoms compatible with CAP: 1) establishing a diagnosis of CAP; 2) determining the initial site of treatment (in- versus outpatient); 3) identifying which microbiologic tests should be performed; and 4) selecting the most appropriate antibiotic therapy. He emphasized that diagnosis cannot be made through patient history and physical examination alone, noting that the gold standard is the presence of an acute radiographic pulmonary infiltrate. “Due to increasing resistance patterns, it is extremely important to establish an accurate diagnosis to prevent the injudicious use of antibiotic therapies,” he explained.

**Failure to perform diagnostic tests  
has resulted in the microbiologic etiology of the  
majority of CAP patients being unknown.**

Employing data from a variety of sources, including the Pneumonia Patient Outcomes Research Team (PORT) prospective cohort study of almost 2300 adults with CAP, Dr. Fine summarized the current state of knowledge regarding CAP. It is a common, costly illness with substantial geographic variation in treatment patterns. Clinicians can now accurately identify patients at increased risk for mortality or other adverse medical outcomes at the time of presentation, based upon an initial history and physical examination as well as limited laboratory testing (Table 2). Failure to perform diagnostic tests has resulted in the microbiologic etiology of the majority of CAP patients being unknown; performance of blood cultures within 24 hours of presentation and timely administration of appropriate antibiotic therapy are both associated with improved 30-day outcomes.

**TABLE 2**  
**VARIABLES ASSOCIATED WITH INCREASED MORTALITY**

- Demographic
- Increasing age
- Patient History Factors/Comorbidities
- Neoplastic disease
  - Congestive heart failure
  - Renal disease
  - Liver disease
  - Cerebrovascular disease
- Physical Examination Factors
- Tachycardia (pulse ≥125 bpm)
  - Systolic hypotension (BP<90 mmHg)
  - Tachypnea (respirations ≥30)
  - Hypo- or Hyperthermia (temperature <35°C or ≥40°C)
  - Presence of altered mental status
- Laboratory and Radiographic Findings
- Arterial pH <7.35
  - Blood urea nitrogen ≥30 mg/dL (11 mmol/L)
  - Sodium <130 mmol/L
  - Glucose ≥250 mg/dL (14 mmol/L)
  - Hematocrit <30%
  - Partial pressure of arterial oxygen <60 mm Hg
  - Pleural effusion

**EPIDEMIOLOGIC STUDIES OF  
COMMUNITY-ACQUIRED PNEUMONIA**

There have been specific changes in the epidemiology of community-acquired pneumonia in the past few decades. First, population-based studies have demonstrated the profound direct effect of aging on both incidence and morbidity related to CAP; secondly, there is a significant seasonal variation associated with CAP. Finally, according to Joseph Plouffe, MD, “there is greater recognition of the ramifications of new pathogens that cause severe pneumonia.” Dr. Plouffe noted that the aging of the population has resulted in a greater overall mortality from pneumonia (Table 3); the growing immunocompromised population has also led to an increased population at greater risk of pneumonia.

**TABLE 3**  
**US PROJECTIONS OF PNEUMONIA INCIDENCE  
AND MORTALITY BY AGE**

Age	Requiring Hospitalization	
	Incidence	Mortality
18-64 years	292,000	15,000
>64 years	532,000	72,000
Overall	824,000	87,000

Marston BJ, Plouffe JF, File TM Jr, et al. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. *Arch Intern Med.* 1997;157(15):1709-1718.

It has long been understood that the incidence of CAP increases during influenza season; research now suggests that pneumonia related to respiratory syncytial virus (RSV) is also more common during the winter months. Both influenza and RSV are cofactors that can lead to a secondary bacterial infection, pneumonia, and hospitalization. Similarly, studies indicate that *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are associated with pneumococcal disease, pneumococcal bacteremia, and pneumococcal pneumonia, particularly among the elderly. The overall mortality rate with bacteremic pneumococcal pneumonia has generally remained constant during the antibiotic era throughout seasonal changes.

Therapy has become complicated as a result of new etiologic agents as well as antibiotic resistance among the classical pathogens. Dr. Plouffe discussed numerous environmental, host, and social factors that have contributed to a growing “at risk” population; as such, he suggested that “clinicians focus on improving the immunity of these populations through influenza and pneumococcal vaccinations.” He also predicted an increased recognition of the role of *Legionella pneumophila* with better diagnostic studies, as well as an increased understanding of the ramifications of *C. pneumoniae*.

**ETIOLOGY AND PATHOLOGY OF  
COMMUNITY-ACQUIRED PNEUMONIA:  
TRADITIONAL AND EMERGING PATHOGENS**

**BACTERIAL PNEUMONIA**

John Bartlett, MD, explained that the “incidence of pneumonia requiring hospitalization has not changed significantly, but the frequency with which the pneumococcus is identified as the etiologic pathogen has plummeted substantially—from approximately 80% during the prepenicillin era to less

than 25% today" (Table 4). Yet, the most commonly detected etiologic agent remains *Streptococcus pneumoniae*.

Other bacterial agents that are common but less frequent than pneumococcus include *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and anaerobes. Rare pathogens include *Enterobacteriaceae*, *Acinetobacter*, and *Pseudomonas*. "Atypical" organisms include *Legionella*, *C. pneumoniae*, and *M. pneumoniae*. The diagnosis of *Legionella* has been facilitated by the development of the urinary antigen and culture; however, lack of consensus on the role of diagnostic tests, as well as differences in findings based upon the different diagnostic tests, has hindered the diagnosis of other atypical organisms. Dr. Bartlett discussed the potential for *Bacillus anthracis* to become an emerging pathogen as a consequence of the threat of biologic warfare or bioterrorism. He acknowledged that this is a highly lethal disease that would not be readily recognized in most health-care facilities, nor would treatment be readily available for the populations that would be affected.

TABLE 4		
CHANGING INCIDENCE OF <i>STREPTOCOCCUS PNEUMONIAE</i> IN US		
	Prepenicillin Era	Current Era
Incidence of hospitalizations	3/1,000	2.5/1,000
Mortality rate	30%	12%
Mortality incidence	100/100,000	30/100,000
% Community-acquired pneumonia caused by <i>S. pneumoniae</i>	80%	<25%

Marston BJ, Plouffe JF, File TM Jr, et al. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. *Arch Intern Med*. 1997;157(15):1709-1718.

### VIRAL PNEUMONIA

While viruses are a common cause of pneumonia in infants and children, they are less common pathogens among adult populations. Stephen Greenberg, MD, noted that "mixed viral/bacterial pneumonia is uncommon among children, yet frequently found among adults. This combination often confounds a diagnosis of viral versus bacterial pneumonia." Dr. Greenberg identified the most typical respiratory and nonrespiratory viruses implicated in community-acquired pneumonia (Table 5), noting that some viruses and their related viral pneumonias are associated with specific seasonal outbreaks (especially November through March). He explained that immunocompromised patients are at increased risk for viral infections/pneumonia, particularly while hospitalized. In fact, viruses have been identified in approximately 10% of hospitalized adult patients with CAP.

Dr. Greenberg explained that primary influenza pneumonia is rare, but it is associated with a high mortality rate. In contrast, "secondary bacterial pneumonias occur with increased frequency following influenza." *S. pneumoniae* is the most common bacterial isolate, although there is also an increased frequency of *S. aureus* pneumonia during influenza outbreaks. Mortality rates for these bacterial pneumonias are significant. Another virus associated with increasing incidence and risk among certain immunocompromised patients is adenovirus pneumonia.

Diagnosis of viral pneumonia requires appropriate specimen collection and laboratory analysis for viral antigen. Dr. Greenberg recommends performing standard tissue culture assays, immunofluorescent staining, EIA, and PCR

TABLE 5	
ETIOLOGY OF VIRAL PNEUMONIA IN ADULTS	
Respiratory Viruses	Nonrespiratory Viruses
Typical	Herpes simplex virus I
Influenza types A and B (winter months)	Measles
Respiratory syncytial virus (winter months)	Hantavirus
Less typical	Cytomegalovirus (CMV)
Parainfluenza virus types 1,2,3	
Adenovirus	
Coronavirus	
Rhinovirus	

assays (if available), as well as serologic tests involving both acute and convalescent sera. He discussed therapeutic approaches, noting that most antiviral agents have not yet been approved for viral pneumonia. "Successful vaccination programs for influenza viruses have been shown to reduce severe influenza-related disease, such as pneumonia, in targeted populations; as such, the development of other antiviral vaccines could markedly change the incidence of viral infections."

**Diagnosis of viral pneumonia requires appropriate specimen collection and laboratory analysis for viral antigen.**

### HOST AND PATHOGEN SUSCEPTIBILITY

"Although the human upper respiratory tract is colonized with approximately 200 different bacterial species, relatively few organisms are able to successfully circumvent different host defense mechanisms to cause disease in the lung," explained Jeffrey Weiser, MD. The most common pathogenic agents, *S. pneumoniae* and *H. influenzae*, exist only in humans; each has the ability to adjust its cell surface to the requirements of different host environments, existing in a form that is well adapted for colonization in the upper respiratory tract and capable of defeating host defenses.

Dr. Weiser noted that all pneumococci are encapsulated, and that the pneumococcus is capable of making 90 distinct capsular polysaccharides. It is the capsular polysaccharide that determines the virulence of the pneumococcus. The cell surface of *Haemophilus* is covered with a human-like carbohydrate as a form of 'molecular mimicry' to decrease its antigenicity and evade immune recognition. Without these structures, the pathogenic organism is sensitive to the bactericidal activity of normal human serum.

### PATHOGEN RESISTANCE IN CAP

#### THE MOLECULAR BIOLOGY OF BACTERIAL RESISTANCE

Alexander Tomasz, PhD, discussed three specific "genetic events" of antibiotic resistance in *S. pneumoniae* and staphylococci that may impact on the management of infections caused by these bacterial pathogens. First, Dr. Tomasz explained how application of molecular fingerprinting techniques facilitated the identification of in vivo capsular switching events, in which clinical isolates of *S. pneumoniae* change their outer-

most surface structures, the polysaccharide capsules. Capsular transformation events [DNA exchange or transformation events] can result in mucosal immunity, may enable the spread of multiresistance, and may cause dramatic changes in virulence. Dr. Tomasz then delineated how “fitness” mutations of penicillin-resistant clinical isolates versus penicillin-resistant laboratory mutants of pneumococci may contribute to the emergence of a few clones with epidemic capabilities. In vivo and in vitro investigations have reported that these specific clinical mutations constructed a completely abnormal bacterial cell wall of penicillin-binding proteins (PBPs) beneath the capsule that was capable of compensating for the inherent risk of modifying targets. While mutant laboratory isolates also developed an abnormal cell wall, it was not as “fit”—the cell wall had reduced growth rate and abnormal morphology. Dr. Tomasz suggested that these mutations occur in natural environments, probably through genetic recombination. Finally, in a recent survey of more than 200 isolates selected for genetic diversity, Dr. Tomasz noted that the genes essential for DNA uptake and recombination were found to be ubiquitous within the pneumococcus.

### PREVALENCE OF RESISTANT BACTERIA

Gary Doern, PhD, acknowledged that there is controversy regarding confidence in the existing epidemiologic data; however, he stated that “there is sufficient information to reliably delineate the current scope and magnitude of the problem of antibiotic resistance with respect to specific outpatient pathogens.” Although he focused on three specific pathogens, namely *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*, he noted that a wide variety of organisms are of concern with respect to the efficacy of antimicrobial therapies. Only *Legionella*, *Mycoplasma*, and *Chlamydia* remain nearly uniformly susceptible to a variety of agents including the macrolides, tetracyclines, and new extended-spectrum fluoroquinolones.

The past 15 years have seen an almost linear increase in the magnitude of the problem of ampicillin resistance with *H. influenzae*. Today, approximately 33% of clinical isolates of *H. influenzae* and almost all *M. catarrhalis* produce beta-lactamase and thus may be resistant to ampicillin and amoxicillin. Rarely, however, are isolates of these two bacteria resistant to other commonly prescribed oral antibiotics.

“Currently, the overall prevalence of intermediate- or high-level penicillin resistance with *S. pneumoniae* is 43.8%, in contrast to only 3.8% in 1988/1989,” noted Dr. Doern. Furthermore, penicillin resistance with *S. pneumoniae* translates, at least to some extent, into cross-resistance with other beta-lactam antimicrobials. There is evidence that the majority of drug-resistant *S. pneumoniae* are represented by a relatively restricted number of clones. He noted that alterations in high molecular weight penicillin-binding proteins explain the proportionate increase in rates of resistance with other beta-lactams. Current national rates of resistance with non-beta-lactam antimicrobials versus *S. pneumoniae* are: macrolides, ~18%; clindamycin, ~4%; tetracycline, ~15%; chloramphenicol, ~3%; trimethoprim/sulfamethoxazole (TMP/SMX), ~25%; and the fluoroquinolones, 0.2%. In addition, data from national surveillance studies indicate that 18% of pneumococci in the United States are multiresistant (resistant to a beta-lactam plus two other classes of antibiotics).

Finally, Dr. Doern noted that “all fluoroquinolones are not created equal.” Ciprofloxacin is somewhat inferior compared to the newer fluoroquinolones (levofloxacin, grepafloxacin, sparfloxacin, and trovafloxacin). Advantages of the newer fluoroquinolones include superior in vitro activity versus *S. pneumoniae* (in the case of grepafloxacin, sparfloxacin, and trovafloxacin) as well as more favorable pharmacokinetic and pharmacodynamic profiles (in the case of levofloxacin, grepafloxacin, sparfloxacin, and trovafloxacin).

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**Advantages of the newer fluoroquinolones include superior in vitro activity versus *S. pneumoniae* as well as more favorable pharmacokinetic and pharmacodynamic profiles.**

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Dr. Doern concluded by stating, “The precise role for the newer-generation fluoroquinolones in the management of CAP remains to be defined. If resistance with alternative agents continues to climb, then no choice will exist. Conversely, the question must be raised as to what will happen to rates of fluoroquinolone resistance, especially with *S. pneumoniae*, if this class of antibiotics becomes more commonly used to treat CAP?”

## CLINICAL MANAGEMENT IMPLICATIONS OF PATHOGEN RESISTANCE IN COMMUNITY-ACQUIRED PNEUMONIA

*Streptococcus pneumoniae* is responsible for the highest incidence of CAP cases, hospitalizations, and mortality, especially among young and older patients (<3 and ≥65 years of age). Concomitantly, it is the pathogen associated with the most dynamic and evolving resistance patterns. Richard Greenberg, MD, suggested that “in order to prevent a Darwinian evolution of disaster, an examination of the clinical management implications of resistance in CAP should focus on *S. pneumoniae*.” He noted increasing rates of *S. pneumoniae* resistance to penicillin, macrolides, and third-generation cephalosporins. In addition, penicillin-resistant *S. pneumoniae* is associated with a very high rate of multidrug resistance. Studies have also shown that prior antibiotic therapy is a predisposing factor for drug-resistant *S. pneumoniae*.

Dr. Greenberg explained that hospitalization may be prolonged in patients with inadequate or inappropriate antibiotic therapy, and such patients will receive additional antibiotic agents, increasing their risk for drug-resistant strains. He noted that antibiotics affect prognosis only after the first few days of the initial diagnosis of CAP. An assessment of oxygenation status is imperative to improve survival rates. He enumerated the clinical concerns as: 1) decreasing the time to identification and susceptibility of the CAP pathogen to less than the current 24 hours, and 2) immediate selection and initiation of appropriate antibiotic therapy. He emphasized that “future therapeutic approaches to the management of CAP will focus on offering a directed treatment based upon an identified pathogen.” Finally, Dr. Greenberg discussed the increasing development of pathogen resistance to ciprofloxacin, in contrast to other fluoroquinolones, noting that “future development of antibiotic therapies should focus not only on efficacy and safety, but also on prevention of drug resistance.”

## THE HOSPITALIZED CAP PATIENT

“Of all the common infections dealt with in clinical practice, pneumonia is by far the most difficult to manage effectively, in great measure because of the challenge of an accurate etiologic diagnosis,” offered Dennis Maki, MD. Approximately 20% of CAP patients require hospitalization, due to increased risk of respiratory failure or other complications associated with high mortality. Once the decision to hospitalize has been made, it is imperative to obtain a sputum gram stain as soon as possible to launch the quest to ascertain the bacteriologic etiology. In addition to a chest radiograph, early microscopic examination of sputum or an aspirate of tracheal secretions can point toward unusual causes, such as undiagnosed HIV infection associated with

*Pneumocystis carinii* pneumonia (PCP), *Legionella* infection, fungal infection (particularly *Cryptococcus* infection), or tuberculosis. Furthermore, the information facilitates pathogen-directed antimicrobial therapy.

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Dr. Maki noted that the average time from arrival at an emergency department until initiation of antimicrobial therapy ranges from 6 to 10 hours in most community hospitals; this delay can have a significant adverse impact on patient outcome. Dr. Maki emphasized that “the challenge is to provide initial therapy within 4 to 6 hours after arrival.” Supportive therapy, particularly for hypoxemia and/or hypercarbic respiratory failure, shock, other organ failure, and electrolyte derangements, can be as important to survival as is anti-infective therapy. Patients who require placement in the intensive care unit (ICU) for monitoring (Table 6) have been shown to have an improved prognosis with management by trained intensivists.

TABLE 6 THE HOSPITALIZED PATIENT WITH CAP: DECISION TO ADMIT TO AN ICU	
Based on the risk factors for increased morbidity and mortality in hospitalized patients with CAP	
American Thoracic Society	British Thoracic Society
RR >30	“Severe” pneumonia
PaO <sub>2</sub> /FIO <sub>2</sub> <250	PO <sub>2</sub> <60
Mech ventilation	PCO <sub>2</sub> >48
Shock	Exhausted, drowsy, or unconscious
Ps<90	Respiratory or cardiac arrest
Pd<60	
Pressors	Shock
Oliguria or ARF	
Niederman MS, Bass JB Jr, Campbell GD, et al. American Thoracic Society. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. <i>Am Rev Respir Dis.</i> 1993;148:1418-1426.	
The British Thoracic Society. Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. <i>Br J Hosp Med.</i> 1993;49:346-350.	

Subsequent management of hospitalized CAP patients includes the continuing evaluation of the patient's response to initial therapy, with reexamination of the diagnosis and suspected etiology if the patient fails to respond. According to Dr. Maki, “The challenge is to determine whether physiologic deterioration reflects true therapeutic failure, or if because of the physiologic consequences of severe infection, the condition is unrelated to therapeutic failure.” Fiberoptic bronchoscopy may facilitate clearer diagnosis in selected cases. Dr. Maki concluded with a discussion regarding the importance of preventing nosocomial infections in hospitalized CAP patients. He recommended using barrier precautions preemptively in critically ill, ventilated ICU patients and other selective high-risk patients who will likely require prolonged hospitalization.

## THE ASSESSMENT AND TREATMENT PATTERNS OF CAP

### AN EMPIRICAL APPROACH

The diagnosis of pneumonia is frequently made in the emergency department based upon confirmation of a new infiltrate demonstrated by chest radiograph. According to David Talan, MD, “Optimal management requires an understanding of appropriate use of diagnostic tests, epidemiology of various pathogens, changing trends in antimicrobial susceptibility, new antibiotic options, and factors determining in- versus outpatient care.” One recent study noted improved survival of elderly pneumonia patients who had more expedient antibiotic initiation; this further emphasizes the important role of the emergency department in the management of CAP.

Ideally, emergency department evaluation of suspected CAP would focus on identifying the causative pathogen prior to initiation of treatment. Realistically, however, this is usually not possible. Instead, the emergency department evaluation most often focuses on establishing the diagnosis of pneumonia, determining the presence of clinical features associated with specific infectious etiologies, and determining whether any other host factors will influence decisions regarding the need for hospitalization and selection of antibiotics (Table 7).

TABLE 7 EMERGENCY DEPARTMENT EVALUATION
<ul style="list-style-type: none"><li>• Establish diagnosis of pneumonia</li><li>• Determine most probable etiology</li><li>• Evaluate comorbidities</li></ul>

In addition to the clinical presentation, the evaluation must include consideration of the character and pattern of symptoms, as well as of the setting in which the pneumonia was acquired; any geographic or animal exposures; and any host factors that could predispose to certain types of infections. For most cases of community-acquired pneumonia, the clinical pattern and exposure history will not be helpful to identify a specific etiology but may occasionally suggest more uncommon infections that require special testing or therapy.

Dr. Talan reviewed some characteristic radiographic findings that are indicative of etiology (Table 8); however, since the radiographic pattern or infiltrate in most cases does not accurately identify etiology, sputum gram stain and culture have been recommended by some experts. However, there are limitations associated with the sputum gram stain test, including the difficulty of obtaining a specimen of sufficient quality and the minority of specimens that demonstrate a predominant organism. Collection of sputum in proper isolation areas is rare in most emergency departments, resulting in the potential spread of *Mycobacterium tuberculosis*. Dr. Talan discussed the lack of correlation with sputum or blood cultures, as well as the rare alterations in therapy based upon the result of the tests. Finally, he explained that the majority of patients have good outcomes with empirical therapy.

Recognizing the limitations of sputum gram stain and culture, Dr. Talan recommended that clinicians utilize the American Thoracic Society (ATS) (Table 9) and Infectious Diseases Society of America (IDSA) CAP Guidelines and base their empirical antibiotic decisions on the known epidemiology of pneumonia, in addition to clinical evaluation. Among adult populations, outpatient cases are most often due to *Mycoplasma* and viruses, whereas inpa-

**TABLE 8**  
**CHARACTERISTIC CHEST X-RAY FINDINGS**

Observation	Etiology
Apical/cavitary	Tuberculosis
Pneumatoceles	<i>Staphylococcus aureus</i>
Multiple opacities	<i>Staphylococcus aureus</i>
Interstitial	<i>Pneumocystis carinii</i> pneumonia
Abscess	Anaerobes

**TABLE 9**  
**AMERICAN THORACIC SOCIETY (ATS) CAP GUIDELINES**

**Empiric therapy to be based on the likely spectrum of pathogens**

- Presence of advanced age or underlying illness
- Severity of illness on presentation
- Inpatient versus outpatient management

**Step 1: Identify patients at low risk for pneumonia**

Age <50  
No cancer, congestive heart failure (CHF), cerebrovascular accident (CVA), renal or liver disease  
Normal mental status  
Pulse <125; Resp rate <30; BP>90; Temp 35°-40°C

**Step 2: Determine Site of Treatment**

Outpatient Care		Short Inpatient Stay	
Age 50-70	0-1 Abnormalities	Age 50-70	2 Abnormalities
Age >70	0 Abnormalities	Age >70	1 Abnormality

Abnormalities: Nursing home, coexisting disease, pH<7.35; Na<130; PaO<sub>2</sub><60 OR sat<90%; BUN>30; Glu>250

Niederman MS, Bass JB Jr, Campbell GD, et al. American Thoracic Society. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis.* 1993;148:1418-1426.

tient cases are frequently caused by *S. pneumoniae* and *H. influenzae*, as well as the atypical pathogens *C. pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella* species. The most severe cases requiring ICU care are predominantly related to *S. pneumoniae*, *S. aureus*, aerobic gram-negative bacilli, and possibly *Legionella*. Clinical evaluation of HIV status, past tuberculosis history or exposure, intravenous drug use, unusual animal exposures, or sick contacts can also provide insight into the etiologic diagnosis.

**It is recommended that clinicians utilize the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) CAP Guidelines and base their empirical antibiotic decisions on the known epidemiology of pneumonia, in addition to clinical evaluation.**

Clinicians must consider expanded antibiotic coverage in light of the increasing resistance associated with CAP pathogens, and particularly of penicillin-resistant *S. pneumoniae*. Dr. Talan acknowledged that the relationship of in vitro resistance with clinical outcome is not yet clear. Nevertheless, he recommended against the use of narrow-spectrum agents in sicker hospitalized CAP patients, suggesting instead the use of the new generation of extended-spectrum fluoroquinolones such as levofloxacin and trovafloxacin. He cited several studies showing that these new fluoroquinolones appear to be clinically superior to second- and third-generation cephalosporins alone or in combination with erythromycin. (Table 10; Table 11, page 8).

**Clinicians must consider expanded antibiotic coverage in light of the increasing resistance associated with CAP pathogens, and particularly of penicillin-resistant *S. pneumoniae*.**

**ETIOLOGIC (PATHOGEN-SPECIFIC) IDENTIFICATION**

Thomas File, Jr., MD, began his presentation by citing the two factors that have significantly impacted the management of CAP over the past few decades: 1) the increasing number of pathogens, and 2) the emerging

**TABLE 10**  
**CAP: LEVOFLOXACIN US MULTICENTER CLINICAL TRIALS**

Drugs and Dosages	Duration (days)	Clinical Responses*	Eradication Rates
Levofloxacin (500 mg QD; IV or PO)	7-14	96%	<i>S. pneumoniae</i> , 100% <i>H. influenzae</i> *, 100%
Ceftriaxone 1-2 mg QD/BID and/or cefuroxime axetil 500 mg BID with optional IV/PO erythromycin or doxycycline	7-14	90%	<i>S. pneumoniae</i> , 97% <i>H. influenzae</i> , 79%

**Atypical Pathogens: Clinical Response**  
(*M. pneumoniae*, *C. pneumoniae*, *L. pneumophila*)  
Levofloxacin: 98%  
Adverse Reactions\*\*  
(nausea or diarrhea)  
Levofloxacin: 6%  
Ceftriaxone/cefuroxime axetil: 9%

\*Statistically significant difference.

\*\*Includes possible or definite relationship to drug.

File TM Jr, Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of IV/PO levofloxacin vs ceftriaxone/cefuroxime axetil in the treatment of adults with community-acquired pneumonia. In: Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans. Washington, DC: American Society for Microbiology; 1996: Abstract LM1.

**TABLE 11**  
**CAP: SPARFLOXACIN US MULTICENTER CLINICAL TRIALS**

Drugs and Dosages	Clinical Response	Bacteriologic Response*	Overall Rate of Drug-Related Adverse Events** (most common event)
<b>Study 1</b>			
Sparfloxacin PO 200 mg QD following 400 mg loading dose	87%	89%	22% (diarrhea-4%)
Cefaclor PO 500 mg TID	84%	79%	25% (diarrhea-5%)
<b>Study 2</b>			
Sparfloxacin PO 200 mg QD following 400 mg loading dose	87%	94%	39% (diarrhea-6%)
Erythromycin PO 500 mg QID	87%	92%	52% (diarrhea-17%)
Sparfloxacin Photosensitivity <ul style="list-style-type: none"> <li>• Reported in 2%-6% of patients</li> <li>• Avoid direct/indirect sunlight while on drug, and up to 5 days afterwards</li> </ul>			

\*Statistically significant difference between the sparfloxacin and cefaclor groups.

\*\*Includes remote, possible, or probable relationship to drug.

Donowitz G, for the SPAR Multicenter CAP Study Group. Treatment of community-acquired pneumonia (CAP) with sparfloxacin (SPAR) and cefaclor (CEF). In: Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans. Washington, DC: American Society for Microbiology; 1996: Abstract LM10.

Bensch G, for the SPAR Multicenter CAP Study Group. Treatment of community-acquired pneumonia (CAP) with sparfloxacin (SPAR) and erythromycin (ERY). In: Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans. Washington, DC: American Society for Microbiology; 1996: Abstract LM12.

resistance of traditional pathogens, particularly pneumococcus. Whereas CAP was overwhelmingly caused by pneumococcal infection and successfully treated with penicillin G 20 years earlier, Dr. File emphasized that "these changes challenge clinicians to utilize agents that more specifically provide appropriate coverage for the underlying etiologic pathogens."

**IDSA Guidelines emphasize  
an etiologic determination  
for appropriate  
antimicrobial selection.**

Dr. File addressed the debate between empiric versus pathogen-directed therapy, focusing specifically on the clinical relevance of an etiologic identification. While the issue remains as to whether an etiologic determination impacts on mortality and morbidity, it is accepted that pathogen-directed therapy can minimize inappropriate or overuse of broad-spectrum antimicrobials, and may reduce the prevalence of drug-resistant strains. He examined the differences between the treatment guidelines established by ATS and IDSA as well as their approaches to microbiologic testing (Table 12). The 1993 ATS Guidelines stratify patients into four different categories based upon severity of illness, age, and underlying conditions; predict the most likely pathogen; and suggest empiric antimicrobial therapy for the predicted pathogen. In contrast, the 1998 guidelines from IDSA integrate the current awareness of resistance, recognizing that even an accurate prediction of pathogen would not reliably translate into an accurate prediction of susceptibility patterns (Table 13). As such, IDSA Guidelines emphasize an etiologic determination for appropriate antimicrobial selection. This would potentially limit the consequences of polypharmacy (eg, cost, resistance, and adverse drug reactions) as well as help identify pathogens of potential epidemiologic significance.

**TABLE 12**  
**CAP GUIDELINES: RECOMMENDATIONS  
FOR ROUTINE MICROBIOLOGIC TESTS**

Microbiologic Test	Outpatients		Inpatients	
	ATS	IDSA	ATS	IDSA
Gram stain	No	Optional	No	Yes
Sputum culture	No	No	No	Yes
Blood culture	No	No	Yes	Yes

Niederman MS, Bass JB Jr, Campbell GD, et al. American Thoracic Society. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis*. 1993;148:1418-1426.

Bartlett JG, Breiman RF, Mandell LA, File TM Jr. Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America. *Clin Infect Dis*. 1998;26:811-838.

**TABLE 13**  
**IDSA CAP GUIDELINES**

Emphasis on identification of causative pathogen with pathogen-specific therapy

- Rational use of microbiologic laboratory
- Pathogen-directed therapy in hospitalized patients
- Prompt initiation of antimicrobial therapy
- Hospitalization based upon prognostic criteria
- Mechanism to update guidelines at regular intervals

Bartlett JG, Breiman RF, Mandell LA, File TM Jr. Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America. *Clin Infect Dis*. 1998;26:811-838.

The utility of diagnostic studies for determining the etiology of CAP remains controversial. In addition to chest radiography, IDSA Guidelines recommend the use of complete blood count (CBC) and chemistry panel, HIV serology, blood cultures, gram stain and culture of sputum, tests for specific pathogens based on risk factors, and thoracentesis if significant pleural fluid is present. Until such time as rapid diagnostic tests such as the polymerase chain reaction (PCR) are developed and available, Dr. File recommended immediate initiation of empiric antibiotics for patients diagnosed with CAP, to be replaced by pathogen-directed therapy upon etiologic diagnosis (Table 14).

**TABLE 14**  
**IDSA: ANTIMICROBIALS FOR *S. PNEUMONIAE***

Agent	Preferred Treatment	Alternative Treatments
Penicillin susceptible MIC* <0.1 µg/mL	Penicillin Amoxicillin	Cephalosporins (cefazolin, cefuroxime, cefotaxime, ceftriaxone, cefpodime, cefprozil)
Intermediate susceptibility MIC 0.1-2 µg/mL	Amoxicillin Cefotaxime or Ceftriaxone	Clindamycin Fluoroquinolone Doxycycline
Penicillin resistant MIC >2 µg/mL	Fluoroquinolones Vancomycin In vitro susceptibility Test results	

\*Minimum inhibitory concentration

Bartlett JG, Breiman RF, Mandell LA, File TM Jr. Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America. *Clin Infect Dis*. 1998;26:811-838.

## DIAGNOSING CAP: TRADITIONAL APPROACHES AND EVOLVING TESTS

"The value of microbial diagnostics depends upon the availability of timely microbiology, the quality of the available microbiology, the accuracy of interpretation, and clinician utilization of the findings," explained Patricia Charache, MD. Among the most important preanalytical, clinician-based steps is the determination of test selection. Dr. Charache recommended using the "simplest approach possible." Specimen source, procurement, and transport are also integral to the efficacy of the test analysis. For example, she reiterated the need to obtain a sputum culture prior to initiation of antibiotic therapy. The need for vaccine-associated programs was also discussed, as was information regarding evolving stains and technological approaches (Table 15), including immunodiagnosics and molecular diagnostics such as fluorescent microscopy and ELISA technology. Dr. Charache explained that these new techniques have been most effective for identifying viral, as opposed to bacterial, pathogens. She emphasized that "in order to achieve microbial diagnosis, it will take a concerted, cooperative effort between the clinician utilizing the laboratory results and the technologists within the laboratory."

**The value of microbial diagnostics depends upon the availability of timely microbiology, the quality of the available microbiology, the accuracy of interpretation, and clinician utilization of the findings.**

**TABLE 15**  
**NEW TECHNOLOGIES FOR CAP DIAGNOSIS**

Immunodiagnosics
Antigen detection tests
Particle technologies
ELISA/EIA technologies
Fluorescence microscopy
Serologies
Molecular diagnostics
Bacteriology
Virology

## THE ACCURATE IDENTIFICATION OF PATIENTS WITH CAP

### CHLAMYDIA PNEUMONIAE

The genus *Chlamydia* comprises a group of intracellular parasitic bacteria with a long, complex life cycle that are now known to cause between 5% to 20% of community-acquired pneumonial infections in adults and children. "The therapeutic implication of the extended life cycle is that multiple-dose regimens need to be utilized," explained Margaret Hammerschlag, MD. She noted that the current methods used for diagnosis of *C. pneumoniae* infection are controversial; they include culture, serology, and PCR/nucleic acid amplification technology.

*C. pneumoniae* must be cultured in tissue, versus cell-free media. Site of specimen collection is important, and culture identification requires 3 to 7 days. Culture confirmation is essential, through fluorescent assay (FA) staining with species-specific monoclonal antibody; Dr. Hammerschlag noted that there is currently no commercially available culture confirmation reagent. Because of these difficulties, the majority of earlier diagnostic evaluations utilized serology, particularly microimmunofluorescence (MIF). MIF criteria for acute infection include a 4-fold rise in IgG, IgG>1:512, or IgM>1:16 (Table 16). However, MIF assay is not standardized, and interpretation is highly subjective. A poor correlation between serology and culture has been observed in children and, to a lesser extent, adults. Dr. Hammerschlag also noted that there are no commercially available nucleic acid amplification assays for *C. pneumoniae*. She suggested that this organism may act more as a cofactor by facilitating a chronic persistent respiratory tract infection or by increasing an individual's susceptibility to infection by another pathogen.

**TABLE 16**  
**SEROLOGIC CRITERIA FOR DIAGNOSIS OF *CHLAMYDIA PNEUMONIAE***

Microimmunofluorescence (MIF)	
Acute infection	4-fold rise IgG IgM≥1:16 IgG ≥1:512
Preexisting antibodies	IgG≥1:16 and <512
Chlamydia complement fixation* (Genus specific)	
Acute infection	4-fold rise ≥1:64

MYCOPLASMA PNEUMONIAE

There have been dramatic changes in knowledge regarding the role of *M. pneumoniae* in CAP. Historically, it was believed that *M. pneumoniae* was primarily responsible for infections in children aged 6 to 21 years; as such, “it was not considered in the differential diagnosis of respiratory disease among other age groups,” according to Gail Cassell, PhD. In addition, *M. pneumoniae* was not considered to be responsible for acute nonfatal bronchopneumonia or for extrapulmonary complications of severe disease. Dr. Cassell noted that the first description of *M. pneumoniae* in the literature included central nervous system (CNS) manifestations.

Dr. Cassell contended that the dearth of reliable diagnostics has resulted in a “lack of appreciation of the disease-producing potential, as well as underdiagnosis of infection, with *M. pneumoniae*.” She reviewed numerous studies on children and adults in which culture and serology produced different diagnostic results. She recommended using PCR (16S and P1 adhesion) and ELISA, with separate IgM and IgG assays (Table 17), along with confirmations by endpoint titration and immunoblotting. Results from two large studies suggest that 12% of patients hospitalized for pneumonia had *M. pneumoniae* as the causative pathogen.

TABLE 17 DETECTION OF IGM AND IGG ANTIBODIES FOR DIAGNOSIS OF MYCOPLASMA PNEUMONIAE INFECTION IN CHILDREN VS ADULTS			
	IgM+ only	IgG+ only	IgM +IgG
Ambulatory children	84%	3%	13%
Ambulatory adults	30%	50%	20%

The severity of complications related to *M. pneumoniae* has also been underestimated. It is associated with morbidity and mortality from pulmonary and extrapulmonary complications that can include CNS involvement, cardiovascular ramifications, and musculoskeletal or dermatologic responses. It may also cause persistent infection. Dr. Cassell concluded by noting that “based upon application of more sensitive diagnostic techniques with verification by culture, it is believed that *M. pneumoniae* morbidity and mortality are greater than previously thought; however, there is currently no good reliable diagnostic method available in the hospital environment or physician’s office for *M. pneumoniae*.”

SPECIAL AT-RISK POPULATIONS FOR CAP

THE ELDERLY

“Pneumonia is the leading infectious disease cause of death in the elderly, and remains one of the top five causes of mortality in persons aged 65 and older,” explained Thomas Yoshikawa, MD. The different aspects of this disease in the elderly as versus younger populations have important consequences on diagnosis, management, and prognosis.

The different aspects of this disease in the elderly as versus younger populations have important consequences on diagnosis, management, and prognosis.

The elderly patient with pneumonia has an elevated risk of impaired cough reflex as well as aspiration, with a consequently lower survival rate.

Immune and pulmonary changes associated with aging may contribute to the increased incidence of pneumonia, and may be associated with the decreased efficacy of vaccines among the elderly. Comorbidities common to the aged also increase the risk of pneumonia. Studies indicate that almost 25% of elderly patients with serious infections do not present with fever. In contrast, there is frequently altered mental status, and presentations involving chest pain and decreased leukocyte counts are common.

Pneumococcal pneumonia is prevalent among the older population; as such, penicillin-resistant *S. pneumoniae* is becoming a concern. The prevalence of chronic obstructive pulmonary disease (COPD) increases the incidence of *H. influenzae* as well as *M. catarrhalis*. Gram-negative bacilli may be more widespread than among younger populations; *Legionella* and *Chlamydia* have also been isolated in older patients. Finally, Dr. Yoshikawa noted that nearly 75% of elderly patients with pneumonia will require hospitalization. He emphasized the importance of obtaining a measurement of oxygen saturation among all elderly patients. In managing the elderly an empiric therapy approach is common. He noted that some hospitals are beginning to use levofloxacin and other new fluoroquinolones to treat CAP in the elderly in light of the prevalence of penicillin-resistant *S. pneumoniae* and atypical organisms as the pathogenic agents. He concluded that “pneumonia in older patients is much more severe, characterized by a different course and prognosis, which then impacts on the approach to therapy.”

THE IMMUNOCOMPROMISED

Henry Masur, MD, began his presentation with an explanation of why the designation of a pneumonia as “community-acquired” may be less useful or even a misleading concept for immunosuppressed hosts than for immunocompetent hosts. Many opportunistic pathogens are acquired in the community. Thus, “community-acquired” does not accurately distinguish between pathogens acquired in the community that overlap with pathogens causing disease in immunocompetent patients, and those causing disease in an immunosuppressed patient.

Among immunocompromised patients, the type of immunosuppression directly impacts on the possible etiologies of pulmonary dysfunction, and therefore on diagnosis and therapy. The spectrum of immunosuppression is heterogeneous, including HIV infection, organ transplantation, congenital immunodeficiencies, and use of cytotoxic drugs and corticosteroid therapies. In addition, the potential for drug interactions and toxicity is far greater than among immunocompetent patients with pneumonia (Table 18).

Given the potential for rapid deterioration, the overwhelming majority of immunosuppressed patients with pneumonia will require hospitalization. In contrast to immunocompetent patients, Dr. Masur emphasized the importance of distinguishing between true pneumonia and other causes of pulmonary dysfunction such as congestive heart failure, pulmonary emboli,

TABLE 18 CAP IN IMMUNOCOMPROMISED PATIENTS	
<ul style="list-style-type: none"><li>• Broader range of etiologies</li><li>• Atypical or subtle presentations</li><li>• More fulminant course</li><li>• Greater risk of drug interactions or toxicities</li><li>• Greater need for identification of causative pathogen</li></ul>	

and drug toxicity. It is also more difficult, but as important, to ascertain whether an identified pathogenic agent or virus is causative within these subpopulations, or merely colonizing the respiratory tract. Response to therapy is not only a function of severity of underlying disease, etiology of pneumonia, and co-infections, but also of the type and extent of immunologic incompetence. The microbiologic workup must be tailored to the specific population. Dr. Masur emphasized that viruses are associated with greater morbidity and mortality among immunocompromised populations. Thus, the need for immediate and accurate diagnosis carries an urgency not necessarily observed in immunocompetent patients.

In commenting on the largest population of immunosuppressed patients—those with HIV infection, Dr. Masur emphasized that except for *S. pneumoniae* and *H. influenzae* organisms, influenza, *Chlamydia*, *Mycoplasma*, *Legionella*, and other traditional “community-acquired pathogens are not common causes of severe pneumonia.” *S. pneumoniae* and *H. influenzae* are also likely to have a high degree of drug resistance when they occur.

### MANAGING CAP: TRADITIONAL AND NEW THERAPIES

Despite the changing etiologies of CAP, pneumococcus remains the most prevalent pathogen (Table 19). Thomas File, Jr., MD, offered a comparison of the traditional/historical approaches to the current management of CAP. “The traditional approach entailed the utilization of selective antimicrobials directed toward a limited number of pathogens, and specifically toward penicillin-susceptible pneumococcus, whereas the new perceptions are empirically using enhanced-spectrum regimens to include coverage for the increasing number of atypical pathogens and drug-resistant strains.” Similarly, an examination shows that the practice patterns for treatment of CAP have evolved over time. Historically, the vast majority of patients were treated with a single drug, predominantly penicillin G, administered intravenously. Over time, the percentage of single-drug approaches decreased from 80% to 50%, with the predominant agent involving a second-generation cephalosporin. Currently, ceftriaxone is the most commonly prescribed agent for CAP, with an increasing utilization of combination therapy (a beta-lactam with a macrolide).

TABLE 19 CHANGING ETIOLOGY OF CAP IN ADULTS		
1970s	1990s	
	Typical Pathogens	Atypical Pathogens
<i>S. pneumoniae</i>	<i>S. pneumoniae</i> * 15%-60%	<i>Mycoplasma</i> 1%-30%
<i>Mycoplasma</i>	<i>H. influenzae</i> * 3%-10%	<i>Chlamydia</i> 5%-30%
	<i>M. catarrhalis</i> * 1%-2%	<i>Legionella</i> 2%-8%
Oral flora	Oral flora*	Viruses 2%-15%
<i>S. aureus</i>	<i>S. aureus</i> * 3%-5%	Fungi
	Gram-negative bacteria* 3%-10%	Mycobacteria*
		<i>Pneumocystis carinii</i> pneumonia
	(No diagnosis 30%-60%)	

\*Increasing resistance.

Doern GV. Trends in antimicrobial susceptibility of bacterial pathogens of the respiratory tract. *Am J Med.* 1995;99(suppl 6B):3S-7S.

In fact, outcomes-based research indicates lower mortality among patients treated with combination therapy (eg, beta-lactam plus macrolide) in contrast to monotherapy (beta-lactam alone). The increased awareness of ‘atypical’ pathogens and the emergence of multidrug resistance of respiratory pathogens require reconsideration of management.

For clinicians concerned with coverage for atypical pathogens, the choice of antibiotic therapies available is narrowed; appropriate agents include the macrolides, the tetracyclines (ie, doxycycline), and new fluoroquinolones.

The clinical relevance of drug-resistant *S. pneumoniae* (DRSP) for pneumonia is debated; recent data are beginning to clarify its significance. One study of bacteremic pneumococcal pneumonia in the United States has revealed that for patients infected with strains with minimum inhibitory concentration (MIC) of  $\geq 2\mu\text{g/mL}$ , there is increased mortality. Vancomycin and the newer fluoroquinolones (levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin) maintain good in vitro activity against *S. pneumoniae* (including penicillin-resistant strains). Dr. File noted that “the newer fluoroquinolones are more appropriately classified as antipneumococcal, based upon their pharmacokinetics and pharmacodynamics.”

Dr. File reviewed studies on the efficacy and safety of the newer therapeutic options. The new fluoroquinolones, including levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin, have been found to have enhanced antipneumococcal activity, especially when DRSP is considered. He noted that “the new fluoroquinolones become first-line agents where there is concern: 1) about resistance, 2) in the more severely ill patients, and 3) regarding immunocompromised patients.” Finally, he discussed future agents under investigation; these include the new glycopeptides, ketolides, and streptogramins. All these agents have shown good in vitro activity against multidrug-resistant *S. pneumoniae*; however, clinical efficacy remains to be determined. Dr. File concluded by noting that “the IDSA emphasis on pathogen identification appears to have clinical significance, as there are likely to be increasing clinical failures among penicillin-resistant cases. Thus, pathogen-directed therapy is to be promoted, based on appropriate diagnostic techniques, whenever possible.”

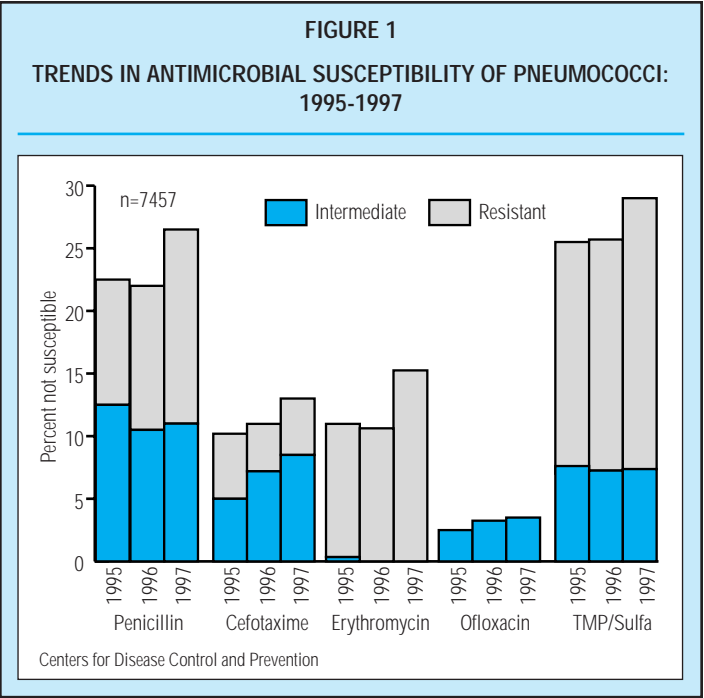
The new fluoroquinolones become first-line agents where there is concern:

- 1) about resistance,
- 2) in the more severely ill patients, and
- 3) regarding immunocompromised patients.

### FUTURE EFFORTS TO TRACK ANTIMICROBIAL RESISTANCE

“The need for more judicious use of antimicrobials cannot be overemphasized,” explained Cynthia Whitney, MD, MPH. As antimicrobial resistance increases, so does the need for accurate surveillance data. Beta-lactam resistance in *S. pneumoniae* was consistently observed beginning in the 1990s. By 1997, nearly one of four strains had reduced susceptibility to penicillin, according to surveillance data from the Centers for Disease Control and Prevention (CDC), with an increasing proportion of highly resistant strains (Figure 1, page 12). Dr. Whitney reiterated the high probability of cross-resistance to antimicrobials. Because of this, “penicillin resistance can be a marker for many other types of antimicrobial resistance among pneumococci.” She noted that data were collected by a CDC sentinel surveillance system from 1979 through 1994; however, the increasing

identification of high-level resistance facilitated utilization of a more aggressive population-based surveillance system. Table 20 lists the different MIC standards for *S. pneumoniae* antimicrobials.



**TABLE 20**  
**NATIONAL COMMITTEE FOR CLINICAL LABORATORY STANDARDS (NCCLS): MIC INTERPRETIVE STANDARDS FOR *S. PNEUMONIAE***

Antimicrobial Agent	Susceptible $\mu\text{g/mL}$	Nonsusceptible	
		Intermediate $\mu\text{g/mL}$	Resistant $\mu\text{g/mL}$
Penicillin	$\leq 0.06^*$	0.1-1.0	$\geq 2$
Cefotaxime	$\leq 0.05$	1.0	$\geq 2$
TMP/SMX	$\leq 0.05$ -9.5	1/19 - 2/38	$\geq 4/76$
Erythromycin	$\leq 0.25$	0.5	$\geq 1$
Vancomycin	$\leq 1$	na	na

\*mcg/mL.

Electronic reporting may facilitate faster and enhanced surveillance data; surveillance systems can be developed specifically for antimicrobial use as well as resistance.

Dr. Whitney discussed the benefits and limitations of current surveillance systems, noting that extrapolating one system's results to different geographic, racial, or age-related populations may not always be accurate. Furthermore, there is a need to begin tracking resistance to cefotaxime

separately from penicillin, as extended-spectrum cephalosporins may still be effective therapy for penicillin-resistant pneumococci infections. She noted that research conducted by the CDC demonstrated "strong correlation between the use of beta-lactams and macrolides among outpatients and pneumococcal resistance; that is, the greater the amount of drug use in a community, the greater the amount of resistance." Electronic reporting may facilitate faster and enhanced surveillance data; surveillance systems can be developed specifically for antimicrobial use as well as resistance. Dr. Whitney also emphasized the need for data that can be "easily interpreted by the clinician making diagnostic and management decisions." Finally, Dr. Whitney noted that the CDC surveillance system is providing preliminary data that will help to address the issue of drug resistance to clinical outcome. The CDC is currently in the process of publishing a study that examined deaths due to bacteremic pneumococcal pneumonia that occurred after the fourth day of illness. The preliminary results from this study, encompassing 1700 patients, demonstrated that patients with high-level resistance (penicillin MIC  $\geq 2$ ) demonstrated a significant risk of increased mortality.

**PATHWAYS FOR THE DEVELOPMENT OF VACCINE INTERVENTIONS FOR CAP**

**VIRAL AND BACTERIAL**

Prevention of viral and bacterial CAP has focused on vaccine interventions, primarily vaccines for influenza virus and *S. pneumoniae*. Each of these currently available vaccines was developed more than 50 years ago and was designed to elicit serum-neutralizing antibodies; utilization rates of both vaccines are less than optimal. John Treanor, MD, explained that while both vaccines are efficacious, "the efficacy rates are relatively lower among those target groups at highest risk of morbidity and mortality, namely the elderly." He noted that one of the greatest complications of influenza is the superimposed bacterial infections that lead to pneumonia.

Dr. Treanor explained the steps involved in the development and use of vaccines. Using influenza as the model, Dr. Treanor reviewed how evaluation of the structure and antigenic diversity of the target antigens provides insight into the potential protective nature of the vaccine in humans (Table 21). For example, antibody to the hemagglutinin is believed to be the major vehicle for protection against influenza from vaccine interventions. Research has indicated protective efficacy levels of 80% to 90% in healthy

**TABLE 21**  
**ANTIGENS INVOLVED IN PROTECTIVE IMMUNITY TO INFLUENZA VIRUS**

Antigen	Role in Protective Immunity
Hemagglutinin	Major neutralizing antigen Protection in adults with HAI $\geq$ 1:40
Neuraminidase	Antibody reduces plaque size "Infection permissive immunity"
M <sub>2</sub>	Antibody reduces plaque size
Matrix	Major targets of cross-reactive CTL
Nucleoprotein	May enhance recovery, limit severity Probably not effective against infection

adults in years when there is a close match between the influenza vaccine antigens and circulating influenza strains. However, the levels of protective efficacy are somewhat lower among the elderly. He discussed the disadvantages regarding the use of embryonated chicken eggs to manufacture influenza vaccines, including concern as to the use of highly pathogenic avian influenza viruses. Alternative substrates have been examined, such as the use of baculovirus-expressed hemagglutinin, with promising results. Research on the pneumococcal vaccine has focused on new protein conjugate pneumococcal vaccines that convert the polysaccharides to a T-dependent antigen.

Since both the current pneumococcal and influenza vaccines are safe and effective, Dr. Treanor pointed out that “public health efforts are appropriately focused on improving vaccination coverage without waiting for further improvement in the efficacy of these vaccines.” Dr. Treanor noted that the current CDC goal is for at least 60% of high-risk/target individuals to receive both vaccinations; until such time as alternative options are available, “the current vaccines are effective and should be used in everyone for whom they are indicated.”

**The current CDC goal is for at least 60% of high-risk/target individuals to receive both vaccinations.**

THE ROLE OF VACCINES

Robert Breiman, MD, emphasized the need for priority development of those vaccines that will have the greatest impact on public health. Use of the current pneumococcal vaccine will prevent between 50% to 70% of pneumococcal bacteremia cases. However, he noted, this “will vary depending upon the population being considered.” He reiterated the efficacy of current vaccinations, but addressed concerns related to the issue of duration of protection as well as the level of protection for those patients at greatest risk for pneumococcal disease. Drawing from data on other vaccinations, he stated that “vaccinating a threshold of patients may protect the unimmunized.” It is believed that the candidate capsular polysaccharide conjugate vaccines currently being evaluated may be a bridge to the “ultimate” vaccine, which would include species-wide and species-specific proteins (Table 22).

TABLE 22
SPECIES-WIDE PROTEIN VACCINE CANDIDATES
Pneumolysin/pneumolysin toxoids
Pneumococcal surface protein A (PspA)
Pneumococcal surface adhesin A (37kD)
Neuraminidase
Autolysin

Recent evaluations of nasally administered, cold-adapted, live attenuated vaccines for influenza illness suggest that these will be quite efficacious, and easy and safe to use; however, these are not yet licensed. Research is ongoing to evaluate recombinant hemagglutinin subunit vaccines. If effective, this approach will make it feasible to design vaccines that are highly specific for circulating epidemic strains.

Dr. Breiman also discussed the scientific basis for vaccines to prevent respiratory syncytial virus, parainfluenza 3, and group A streptococci. He indicated substantial interest in vaccines against *M. pneumoniae*, *C. pneumoniae*, and *M. tuberculosis*. There has been particular progress in the area of tuberculosis vaccines, for which more than 100 candidates are currently undergoing laboratory evaluation. He concluded that the “future of respiratory vaccines is bright.” Emphasis will be not only on the development of safe and effective vaccinations, but also on packaging the different vaccinations in combinations that would facilitate greatest ease of administration, compliance, and affordability.

**Emphasis will be not only on the development of safe and effective vaccinations, but also on packaging the different vaccinations in combinations that would facilitate greatest ease of administration, compliance, and affordability.**

EVOLVING ISSUES IN CAP

THE ROLE OF MANAGED CARE

The emphasis of cost containment in most managed care organizations is challenged by the high-volume, high-admission rates, high cost, and high variability in treatments related to community-acquired pneumonia. According to Neil Massoud, PharmD, MBA, FCCP, the focus of managed care organizations has been on increasing outpatient management and optimizing use of antibiotics. Ideal practice guidelines must integrate a variety of factors, including compliance issues, epidemiology, age, gender, risk factors, cost, and the evidence-based literature. Dr. Massoud discussed the development of the Best Practice Guidelines for Pneumonia as a tool/system by which primary care physicians and other clinicians can optimize their treatment of pneumonia. Recognizing that pharmacology is not as great a cost factor for pneumonia as is, for example, depression, the approach has focused on improving quality indicators that could improve clinical outcomes. These might include factors to help identify candidates for the pneumovax, use of oral versus parenteral drugs to facilitate earlier hospital discharges, and integration of epidemiologic data to enhance pathogen-specific treatment.

**Ideal practice guidelines must integrate a variety of factors, including compliance issues, epidemiology, age, gender, risk factors, cost, and the evidence-based literature.**

FORMULARY DECISION MAKING IN CAP

Joseph Bertino, Jr., PharmD, addressed the considerations for formulary drug selection in the treatment of CAP. Variables to be considered include bacterial spectrum, proven efficacy, pharmacokinetics and pharmacodynamics, toxicity, development of resistance, convenience in dosing, and cost (Table 23, page 14). The components of formulary decision making include efficacy in resolving the infectious process; efficacy in eradicating the organism; efficacy in preventing resistance; and finally, avoidance or

**TABLE 23**  
**CONSIDERATIONS IN THE**  
**SELECTION OF ANTIBIOTICS IN CAP**

- Activity of antibiotic against common pathogens  
Emphasis on local susceptibility patterns
- Comparative clinical trial data
- Pharmacodynamics of agents  
Efficacy, toxicity, and effect on bacteria
- Pharmacokinetics of agent
- Development of resistance (durability)
- Cost
- Convenience

reduction of toxicity. Dr. Bertino recommended that prior to utilizing any national guidelines, practitioners must first consider local susceptibility patterns. The most commonly used therapeutic agents include the beta-lactams, fluoroquinolones, and macrolides, because of their broad-spectrum coverage. He noted the absence of comparative trials of the newer agents, resulting in efficacy comparisons utilizing the older agents.

**The components of  
formulary decision making  
include efficacy in resolving the  
infectious process; efficacy in eradicating  
the organism; efficacy in preventing  
resistance; and finally,  
avoidance or reduction of toxicity.**

The pharmacokinetics of an agent impact on the dosing regimens (Table 24). Preferred dosing regimens are once or twice daily, such as seen with the newer fluoroquinolones and macrolides. In addition, drugs that are highly white blood cell-concentrated, such as azithromycin, may be used at higher doses for shorter treatment durations (1-3 days). The most important pharmacodynamic parameters to consider are dependent on the agent. For beta-lactam antibiotics, macrolides, and clindamycin, time above the MIC ( $T > MIC$ ) is of primary importance. The AUC/MIC ratio has been shown to be

**TABLE 24**  
**PHARMACOKINETICS OF ANTIBIOTICS**

<b>Antibiotics Correlated With <math>T &gt; MIC^*</math></b>	<b>Antibiotics Correlated With 24-hr AUC/MIC<sup>**</sup></b>
Penicillin	Aminoglycosides
Cephalosporins	Fluoroquinolones
Carbapenems	Azithromycin
Monobactams	Tetracycline
Macrolides	Vancomycin
Clindamycin	Quinupristin-Dalfopristin
<b>Antibiotics Correlated With <math>C_{max}/MIC^†</math></b>	
Aminoglycosides	
Fluoroquinolones	

\* Time above minimum inhibitory concentration.

\*\* 24 hr Area under curve/minimum inhibitory concentration.

† Peak tissue levels/minimum inhibitory concentration.

predictive for aminoglycosides, fluoroquinolones, azithromycin, tetracyclines, vancomycin, and quinupristin-dalfopristin. Finally, peak-to-MIC ratio is an important predictive dynamic parameter for the fluoroquinolones and aminoglycosides. Studies on levofloxacin indicate that as the peak-to-MIC ratio increases, so does the probability of microbiologic eradication. Questions remain as to how pharmacodynamic profiles correlate with clinical outcome, as well as whether pharmacodynamic optimization reduces the development of resistance.

Dr. Bertino cited research that found an increase in noncompliance directly proportionate to the dosing schedule, with compliance highest for once-a-day regimens. He suggested that this be considered for future drug development, as well as within the formulary decision-making process. Finally, he commented on the lack of data on cost effectiveness, noting that although older agents may be relatively less expensive than newer agents, costs related to toxicity and antibiotic resistance are often not considered.

## CONCLUSIONS

Community-acquired pneumonia affects 4 million individuals annually. Thus the many challenges facing clinicians who assess and manage patients with community-acquired pneumonia need to be appropriately addressed. While *S. pneumoniae* remains the most commonly detected pathogen, emerging pathogens such as *M. pneumoniae*, *C. pneumoniae*, and *Legionella* have been identified as causative in increasing numbers of patients with CAP. In light of the emergence of these pathogens, the therapeutic management of patients with CAP needs to be reexamined. Antimicrobial resistance to traditional, as well as newer agents, is increasing. There are significant levels of intermediate- or high-level resistance of *S. pneumoniae* to the beta-lactams and macrolides.

Consequently, there is a growing trend toward treating patients based on pathogen specificity, as opposed to an empirical approach. When empiric treatment is necessary, the use of therapeutic agents, such as the newer extended-spectrum fluoroquinolones that can provide coverage for traditional as well as emerging pathogens, is an attractive option. It is also important that candidates for pneumococcal vaccination receive this preventative therapy. By addressing these clinical issues, it is hoped that the morbidity and mortality associated with CAP is reduced, and that the injudicious use of antibiotics is decreased.

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# COMMUNITY-ACQUIRED PNEUMONIA IN ADULT AND ELDERLY POPULATIONS

## ANSWER SHEET, PROGRAM EVALUATION, AND CME CREDIT REQUEST

The National Institutes of Health/Foundation for Advanced Education in the Sciences is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

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### POST-TEST ASSESSMENT - PLEASE CIRCLE THE CORRECT ANSWER

- For which of the following patients should hospitalization be considered?
  - 62 years old, respiratory rate <30/minute, modest comorbidities
  - 48 years old, hematocrit <30%, modest comorbidities
  - 72 years old, normal mental status, modest comorbidities
  - 43 years old, arterial hypoxemia, no comorbidities
- At present, the most accurate diagnosis of CAP can be determined through:
  - Physical exam
  - Patient history
  - Chest radiograph
  - None of the above
- Since 1988/1989, the level of intermediate or high-level penicillin resistance with *S. pneumoniae* has risen to \_\_\_\_\_.
  - 6.8%
  - 43.8%
  - 10.5%
  - 25%
- Benefits of the newer fluoroquinolones include:
  - Improved pharmacokinetics
  - Greater in vitro activity against *S. pneumoniae*
  - Better pharmacodynamic profile
  - All the above
- In the adult population, most CAP outpatient cases are due to:
  - S. aureus*
  - Mycoplasma*
  - Viruses
  - b and c
- Outcomes for patients hospitalized with CAP can be affected by:
  - Inappropriate therapy
  - Delays in the ER
  - Nosocomial infections
  - All the above
- Which of the following is considered to be an atypical CAP pathogen?
  - M. pneumoniae*
  - H. influenzae*
  - Oral anaerobes
  - S. pneumoniae*
- According to the American Thoracic Society Guidelines for the management of CAP, what parameters should be considered for initial treatment?
  - Severity of illness and history of prior antibiotic treatment
  - Need for hospitalization, severity of illness, and patient age
  - Patient age, most probable causative pathogen, and severity of illness
  - Comorbidity, severity of illness, and probably etiology
- Utilization of the current pneumococcal vaccine will prevent pneumococcal bacteremia in what percentage of cases?
  - 30% - 40%
  - 50%
  - 50% - 70%
  - 80%
- Which pathogen causes most CAP cases, hospitalizations, resistance, and mortality?
  - S. pneumoniae*
  - S. aureus*
  - Legionella*
  - C. pneumoniae*

### EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for future activities of this type.

- |                                       | Excellent | Good  | Fair  | Poor  |
|---------------------------------------|-----------|-------|-------|-------|
| 1. How would you rate (please check): |           |       |       |       |
| a. Value of the topic                 | _____     | _____ | _____ | _____ |
| b. Relevance to your practice         | _____     | _____ | _____ | _____ |
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2. Were the goals and objectives clearly stated: ☐ Yes ☐ No

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6. Additional comments and/or suggested topics for future CME activities.

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